Communication, and applicants expressly reserves the right to bring the subject matter of the original claims again in a subsequent, related application.

Claims 28 and 29 have been rejected for the following reasons.

The Examiner has rejected claims 28 and 29 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the invention was filed, had possession of the claimed invention.

The Examiner has rejected claims 28 and 29 under 35 U.S.C. §112, first paragraph, asserting that the specification contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The Examiner has provisionally rejected claims 28 and 29 under the judicially created doctrine of double patenting over claim 14 of co-pending application no. 09/738,968. This is a provisional double patenting rejection because the conflicting claims have not yet been patented.

These rejections are believed to be overcome in view of the amendments and arguments discussed below.

Amendment of the Claims

Support for the amendments to claim 28 can be found throughout the specification as originally filed, for example, at the following locations: page 5, lines 21-24; page 65, line 9, to page 67, line 6; and Figure 12.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

Addressing the Examiner's Rejections

1. Rejection Of Claims 28 and 29 Under 35 U.S.C. §112, First Paragraph, Written Description.

The Examiner has rejected claims 28 and 29 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the invention was filed, had possession of the claimed invention.

The Examiner asserts the following:

> However, the specification does not describe the phenotype and characteristics of the transgenic mice that comprised the recited construct. The specification does not provide any description as to whether all the cells of the transgenic mice would express the reporter gene or whether a certain cell type would express the reporter gene and what would be the effect of expressing the transgene on the transgenic mouse development. (Office action, dated 13 March 2002, page 3, lines 8-13.)

The Examiner goes on to assert the following:

> In other words, with the limited information disclosed in the specification, an artisan would have not been able to predict [whether (*sic*)] the phenotype of the recited transgenic mice. (Office action, dated 13 March 2002, page 3, lines 28-31.)

First, the applicants would like to point out that the "phenotype" of the transgenic animals of the claimed invention is the ability to express a light-generating protein, wherein expression of the light-generating protein is regulated by a specific VEGFR-2-derived, cis-acting transcriptional regulator. In this case, the light-generating protein is acting as a reporter sequence. The specification clearly teaches how to detect expression of the light-generating protein in cells or transgenic animals (see, for example, pages 22-23 where different light-generating reporters are taught, and pages 20-21, and 45 where methods of monitoring expression of a light-producing reporter are described). Accordingly, applicants submit that the specification clearly teaches the expected phenotype of the claimed transgenic mice and how to monitor the phenotype.

Second, the claimed transgenic mice of the present invention are not gene knock-outs. U.S. Patent Nos. 5,464,764 and 5,487,992 describe transgenic animals in which a gene of interest is deleted or mutated sufficiently to disrupt its function -- such "knock-out" animals are made by taking advantage of the phenomena of homologous recombination. (*See, also* U.S. Patent Nos. 5,631,153 and 5,627,059). Using the "knock-out" approach, when the vector is introduced into the embryonic stem cell, a sequence becomes integrated into a target gene in the genome via homologous recombination. The integration disrupts the function of the target gene and allows for examination of the phenotype resulting from the disruption of the gene. However, in the presently claimed invention gene disruption is not the means by which a phenotype is being identified; rather, as described above, the phenotype is created by introducing a reporter gene into the transgenic animal, wherein expression of the reporter gene can be evaluated non-invasively in living, transgenic mice.

Further, the Examiner asserts the following:

> It is note (*sic*) clear whether the transgenic mice which was made using the transcription regulator of SEQ I DNO 32 (*sic*) alone (without the enhancer) would have had the same phenotype. (Office action, dated 13 March 2002, page 3, lines 23-25.)

In view of the above information, the applicants submit that the "phenotype" (that is, the ability to express a light-generating protein and observe the production of light mediated by the expressed light-generating protein) would in fact be the same phenotype. The only difference may be a difference in expression pattern as a result of the presence or absence of the enhancer sequence. However, the specification provides clear guidance to one of ordinary skill in the art about the methods of monitoring expression of the light-generating reporter protein (i.e., expression of which results in the observable phenotype). Compliance with the written description requirement is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Applicants submit that the specification provides sufficient guidance for one of ordinary skill in the art to see that the inventor, at the time the invention was filed, had possession of the claimed invention.

In an effort to facilitate prosecution the applicants have amended independent claim 28 to include the presence of the enhancer sequence.

In view of the above amendments and arguments, applicants submit that the claims comply with the requirements of 35 U.S.C. §112, first paragraph, and respectfully request withdrawal of this rejection of the claims.

2. Rejection Of Claims 28 and 29 Under 35 U.S.C. §112, First Paragraph, Make and/or Use.

The Examiner has rejected claims 28 and 29 under 35 U.S.C. §112, first paragraph, asserting that the specification contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

First, the Examiner asserts the following:

> It is noted that the specification teaches to insert a VEGFR-2 enhancer sequence to the vector comprising the SEQ ID NO 32 and use the resultant vector in making a transgenic mouse. Therefore, it is not clear whether a transgenic mouse recited in claim 28 could have been made that expressed the reporter protein in the absence of the enhancer of the VEGFR-2. However, the specification does not describe the phenotype and characteristics of the transgenic mice that comprised the recited construct. The specification does not provide any description as to whether all the cells of the transgenic mice would express the reporter gene or whether a certain cell type would express the reporter gene and what would be the effect of expressing the transgene on the transgenic mice development. While the art of making a transgenic mouse has become routine and therefore, an artisan would have been able to make the transgenic mouse as claimed, the next question is, in the absence of any phenotype of characteristics, would an artisan of skill have been able to use the claimed transgenic mouse. (Office action, dated 13 March 2002, page 5, lines 11-25.)

Applicants submit that the specification teaches vectors useful for generating transgenic mice in the absence of the enhancer sequence (see, for example, page 3, line 8, to page 4, line 3; page 56, lines 9-16; pGL3B2-KP, Figure 12). Further, as the Examiner has noted "the art of making a transgenic mouse has become routine." Accordingly, the

only remaining issue is whether the specification teaches one of ordinary skill in the art how to use the invention.

Second, the Examiner asserts the following:

> It is note (*sic*) clear whether the transgenic mice which was made using the transcription regulator of SEQ I DNO 32 (*sic*) alone (without enhancer) would have had the same phenotype. The specification neither describes these characteristics nor it discloses as to what characteristics could be expected in the mouse and whether the characteristics observed in the transgenic mice of the declaration were to be expected. It is noted that for an artisan (*sic)* would have required the characteristics of the transgenic mice for its intended use in identifying compounds that alter angiogenesis or that alter the expression of VEGFR-2 promoter, however, in the absence of any guidance regarding the phenotype of the mouse, an artisan would not have been able to use the mouse. (Office action, dated 13 March 2002, page 6, lines 4-14.)

As noted above, the phenotype of the claimed transgenic mice is the ability to produce light, wherein the light-production is mediated by a light-generating protein whose expression is under the control of the specific VEGFR-2 cis-acting transcription regulator. The relevant characteristics of such mice were described in the specification (e.g., page 20, line 8, to page 21, line 17). Primarily the characteristic of interest, in the context of identifying compounds that alter angiogenesis, is examining the effects of such compounds on the level of light produced by the mice, i.e., are the cis-acting transcription regulatory sequences being affected (for example, by up or down regulation). The specification teaches one of ordinary skill in the art the relevant VEGFR-2 sequences (e.g., pages 55-57, pages 65-66, Figure 12), useful vectors (e.g., Example 3, Figure 12, page 22, line 1, to page 23, line 20), and how to monitor expression of a light-generating reporter protein, non-invasively, in living mice (e.g., pages 20-21, and 45). Methods of making transgenic animals are well established as noted by the Examiner. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Accordingly, the applicants submit that one of ordinary skill in the art would have

been able to make and use the transgenic mice of the present invention in view of the teachings of the specification and information known in the art.

The Examiner goes on to assert the following:

> Furthermore, since the targeting vector contains a reporter gene, its insertion in the genome of the mice would result in the disruption of the expression of the VEGFR-2 protein and it is not clear as to what would be the effect of the loss of VEGFR-2 protein on the transgenic mouse. (Office action, dated 13 March 2002, page 6, lines 14-17.)

The vectors described in Figure 12 are not targeting vectors (examples of targeting vectors are shown in Figures 13 and 14). The vectors described in Figure 12 are not vectors that would typically be useful for disruption of a target gene. The only mouse sequences in the vector are VEGFR-2 regulatory sequences. As noted in the declaration (Declaration of Dr. Zhang, page 3, paragraph 7) the transgene has multiple chromosomal locations as is typical. The specification does describe a method of generating transgenic animals wherein a targeting vector is employed. However, the specification clearly teaches that such targeting vectors are typically targeted to suitable single copy non-essential genes (e.g., specification, pages 31-40). Non-limiting examples of targeting sequences for use in generating transgenic mice include sequences obtained from or derived from vitronectin, Fos B and galactin 3 (specification, page 32, lines 1-2). VEGFR-2 is not identified as a "suitable single copy non-essential gene" and no targeting constructs are described to disrupt the VEGFR-2 gene. Accordingly, the issue of disruption of the expression of the VEGFR-2 protein is moot.

Finally, the Examiner asserts the following in the context of the teachings of Wood (Comparative Medicine 50(1):12-15, 2000):

> This clearly indicates that the phenotype of the transgenic mice is unpredictable and the specification does not provide any guidance regarding the phenotype of the claimed transgenic mouse and therefore, an artisan of skill would have required extensive experimentation to determine the effects of expressing the vector construct comprising SEQ ID NO 32 and to use them in screening for compounds that alter angiogenesis and such experiments would

> have been undue since the phenotype of the transgenic mice unpredictable (*sic*). (Office action, dated 13 March 2002, page 6, line 28, to page 7, line 3.)

The present claims are directed only to transgenic mice, not to methods for screening for compounds that alter angiogenesis. As discussed above, the relevant phenotype of the claimed transgenic mice is the ability to produce light, wherein the light-production is mediated by a light-generating protein whose expression is under the control of the specific VEGFR-2 cis-acting transcription regulator. The reference cited by the Examiner deals with phenotypic assessment of genetically modified rodents, where the assessment has two stages. The primary level of assessment is to find abnormalities. The secondary level of assessment is to quantify and evaluate the abnormalities detected. The reference is not addressing the use of reporter constructs, rather it is addressing the use of rodents having mutations that give rise to particular phenotypes. The phenotype of interest in the present transgenic mice is light-production. The mice are useful in the methods described by the Examiner; however, the phenotype being screened is light production as a "surrogate" reporter for angiogenesis, not any angiogenesis-disruption related phenotype. In fact, the present invention, provides a valuable alternative to standard genetic modification of rodents (e.g., knock-out mutations) by use of the light-reporter system that can be monitored non-invasively in living animals.

The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). As described above the applicants have provided a great deal of guidance concerning the generation and use of the transgenic animals of the present invention.

In view of the above amendments and arguments, applicant submits that the claim complies with the requirements of 35 U.S.C. §112, first paragraph, and respectfully requests withdrawal of the rejection of the claims.

3. Provisional Rejection of the Claims Under the Judicially Created Doctrine of 35 U.S.C. §102

The Examiner has provisionally rejected claims 28 and 29 under the judicially created doctrine of double patenting over claim 14 of co-pending application no. 09/738,968. This is a provisional double patenting rejection because the conflicting claims have not yet been patented.

Claim 14 is no longer pending in USSN: 09/738,968. The pending claims in that application are claims 18-30 which are directed to isolated polynucleotides, expression cassettes, vectors, and cells comprising polynucleotide sequences derived from SEQ ID NO:44 which is a 6 kb promoter region derived from the VEGF mouse gene (not the VEGFR-2 mouse gene that is claimed in the present application). The Examiner restricted claims 18-30 into a group different from the group in which claim 14 falls. Claims 1-17 and 31-93 have been cancelled in USSN: 09/738,968. Accordingly, the inventions in these two applications are independent and distinct.

In view of the above arguments applicants submit that the claims comply with the requirements of 35 U.S.C. §101, and respectfully request withdrawal of this rejection of the claims.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §101, §112, and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 325-7812.

Please direct all further communications in this application to:

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Respectfully submitted,

Date: 4 Sept 2002

By: Gary R Fabian

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APPENDIX A

Marked-up Version of the Claims as Amended herein.

28. (Amended) A transgenic mouse or progeny thereof, comprising an expression cassette comprising a cis-acting transcription regulator operably linked to a reporter sequence encoding a light-generating protein, wherein said cis-acting transcription regulator consists of the sequence presented as SEQ ID NO:35 and the sequence presented as SEQ ID NO:32.

29. The transgenic mouse of claim 28, wherein said light-generating protein is a luciferase.

[redacted]

APPENDIX B

What is claimed is:

28. A transgenic mouse or progeny thereof, comprising

an expression cassette comprising a cis-acting transcription regulator operably linked to a reporter sequence encoding a light-generating protein, wherein said cis-acting transcription regulator consists of the sequence presented as SEQ ID NO:35 and the sequence presented as SEQ ID NO:32.

29. The transgenic mouse of claim 28, wherein said light-generating protein is a luciferase.